Got the Munchies for an Egg Sandwich? The Effects of Cannabis on Bowel Motility and Beyond

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The use of medicinal cannabis has a long history dating back thousands of years. Recent discoveries have shed light on its mechanism of action with the identification of cannabinoid receptors and endocannabinoids, which make up the body's endocannabinoid system. Cannabinoid receptors, particularly the cannabinoid 1 and 2 receptors, play a crucial role in modulating the gut–brain axis and serve as potential therapeutic targets for gastrointestinal motility and inflammatory disorders. With increasing legalization of cannabis and a rising number of users, understanding the effects of cannabis on gut motility is essential for nuclear medicine providers. Although tetrahydrocannabinol, the principal psychoactive constituent of cannabis, may decrease gut motility in experimental settings, it appears to paradoxically improve symptoms in gastroparesis. Treatment effects are difficult to measure given the large number of variables that could significantly alter outcomes, such as cannabinoid type, potency, and route of intake. Another consideration is the highly personalized gut microbiome, which directly interacts with the endocannabinoid system. Further research is required to delineate these multifaceted, complex cannabinoid interactions. The goal of this article is to explore the knowns and unknowns of the impact of cannabis on the alimentary system.

Key Words: gastric emptying; bowel motility; gastroparesis; cannabis; marijuana; gut microbiome

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The use of cannabis can be traced back for millennia. Descriptions of its use for recreational, spiritual, and medicinal purposes have been recorded in ancient texts all over world, such as the Ebers Papyrus from 1550 BCE, which describes its topical application for inflammation (*1*). Despite the long history of cannabis as a medicinal herb, we have only recently begun to understand its mechanism of action. In 1988, the first cannabinoid receptor was identified as a binding site for tetrahydrocannabinol (the principal psychoactive component of cannabis) in the brain (*2*). This discovery led to the identification of endogenous cannabinoids synthesized within our own bodies that regulate the broader endocannabinoid system. The system comprises endocannabinoid substrates (anandamide and 2-archidonoyl glycerol), cannabinoid receptors (primarily the cannabinoid 1 [CB1] receptor and the cannabinoid 2 [CB2] receptor), and other components of the gut–brain axis (Fig. 1).

The CB1 and CB2 receptors are principally responsible for modulating the gut–brain axis. CB1 receptors, located centrally in the dorsal vagal complex of the brain, are responsible for emesis via the vagus nerve. CB1 receptors, located peripherally throughout the intestinal tract, modulate motility. CB2 receptors are found primarily in inflammatory cells lining the gastrointestinal tract and in the peripheral nervous system. Both receptors have been identified as potential therapeutic targets in functional gastrointestinal disorders and inflammatory bowel disease (*3*).

With expanding legalization of cannabis, use has become increasingly more common in the United States. As of 2023, 38 states allow the medical use of cannabis, 23 states allow the recreational use of cannabis, and 9 states allow cannabis with a low-tetrahydrocannabinol–to–high-cannabidiol ratio. Only 3 states, that is, Idaho, Nebraska, and Kansas, lack a public access cannabis program (*4*). According to the 2021 National Survey on Drug Use and Health, 18.7% of people 12 y or older (52.5 million people) used marijuana, with the rates being highest among young adults 18–25 y old (35%) (*5*). With increased accessibility and surging user population, understanding the effects of cannabinoids on gastrointestinal motility is essential for physicians who treat and manage patients with gastrointestinal disorders.

Although the gastroenterology literature has described the effects of cannabinoids on the gut, there is a paucity of research in the field of nuclear medicine. This continuing education article attempts to examine and summarize our current knowledge on this complex topic and provide

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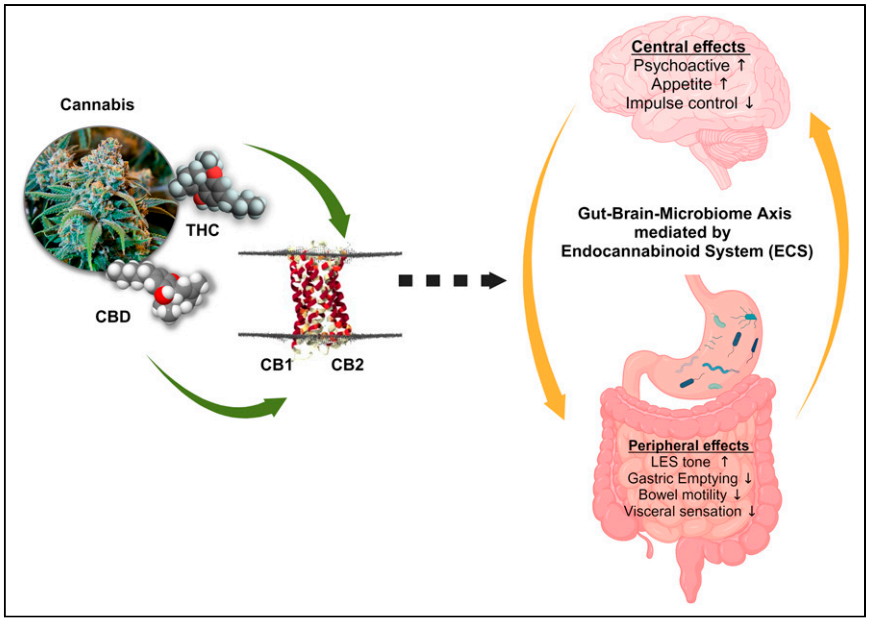

FIGURE 1. Primary effects of cannabis on human body. Principal phytocannabinoids (tetrahydrocannabinol and cannabidiol) interact primarily with CB1 and CB2 receptors found in brain and gastrointestinal tract. These receptors, combined with endocannabinoids, define endocannabinoid system, which mediates complex bidirectional interactions among gut, brain, and microbiome (*43–46*). CBD = cannabidiol; LES = lower esophageal sphincter; THC = tetrahydrocannabinol. (Created with BioRender.com; cannabis image courtesy of Cannabis Training University [https://creativecommons.org/licenses/by-sa/4.0/].)

recommendations for gastric emptying and bowel transit scans performed in an era with near-ubiquitous cannabis access.

Gastric emptying scintigraphy (GES) remains the primary imaging modality for evaluating functional disorders of the stomach. The procedural standard of the Society of Nuclear Medicine and Molecular Imaging has become a useful benchmark to define abnormal delayed gastric emptying. First, it is important to distinguish delayed gastric emptying from gastroparesis—terms that are not synonymous. Gastroparesis is a clinical condition for which delayed gastric emptying is used as one of several required diagnostic criteria. Gastroparesis requires characteristic symptomatology (nausea, vomiting, regurgitation, dyspeptic symptoms) and the absence of gastric outlet obstruction. Although gastroparesis is commonly attributed to idiopathic or diabetic causes, numerous conditions that mimic gastroparesis can also demonstrate delayed gastric emptying. The differential diagnosis for delayed gastric emptying includes functional gastrointestinal disorders, gastroesophageal reflux disease, medications, postsurgical states, eating disorders, connective tissue disease (scleroderma), neuromuscular conditions (myasthenia gravis), neurodegenerative conditions (Parkinson), and neuropsychiatric conditions (stress, anxiety). Such functional disorders defined by the Rome IV criteria include functional dyspepsia, rumination syndrome, cyclic vomiting syndrome, and cannabinoid hyperemesis syndrome (*6*,*7*). Since patients may use cannabis recreationally or self-medicate for these specific conditions, understanding the physiologic effects of cannabis is essential for accurate interpretation of GES.

LET'S GET INTO THE WEEDS: DEFINING CANNABIS, CANNABINOIDS, AND NOMENCLATURE

Because of the variety of cannabis plants and cannabinoid compounds, we will first review some definitions and nomenclature. *Cannabis sativa, Cannabis indica,* and *Cannabis ruderalis* are the primary plant species from which commercial cannabis is derived. These plants are known by many other street names, such as marijuana, Mary Jane, weed, pot, grass, ganja, hash, and purple haze, to name a few. Inhalation of smoked cannabis is the most common form of intake.

The principal psychoactive component of cannabis is δ-9-tetrahydrocannabinol, which activates CB1 receptors and decreases bowel motility. The other primary cannabinoid of interest is cannabidiol, which may have desirable antiinflammatory effects and play a role in motility. There are approximately 80 other naturally occurring, plant-based phytocannabinoids within cannabis whose actions continue to be studied.

Pharmaceutical (synthetic) tetrahydrocannabinol includes drugs such as dronabinol (Marinol; Unimed Pharmaceuticals), which shares the same chemical structure as organic tetrahydrocannabinol found in cannabis. It has been approved by the U.S. Food and Drug Administration for appetite stimulation in HIV/AIDS anorexic patients and treatment of chemotherapy-induced nausea and vomiting. It is also used off-label for innumerable other illnesses. A pharmaceutical synthetic form of cannabidiol also exists (Epidiolex; Jazz Pharmaceuticals), which has been approved for rare intractable seizure disorders. Hemp is legally defined in the United States as all other parts of the cannabis plant, such as the fibrous stem, which contain less than 0.3% tetrahydrocannabinol and are used in various industrial products.

Synthetic (neo)cannabinoids have an altered chemical structure but mimic the effect of tetrahydrocannabinol on cannabinoid receptors. These drugs were marketed as "legal highs" or "fake weed" and became popular in the early 2000s because of their commercial availability and undetectability on drug tests. Common product names include K2 and Spice. Early synthetics are now illegal because of their unregulated status and dangerous potency, but newer

agents continue to enter the market. Drug companies are attempting to synthesize new, safer formulations (*8*).

Endocannabinoids are lipid substrates made endogenously by the human body. Anandamide was first discovered in 1992 and was characterized as a neurotransmitter. The more recently discovered endocannabinoid is 2-archidonoyl glycerol. It is now known that the action of these endocannabinoid bioactive lipids extends far beyond the central nervous system. Beyond their function at the CB1 and CB2 receptors, anandamide and 2-archidonoyl glycerol also interact with a multitude of other receptors such as transient receptor potential vanilloid type 1, peroxisome proliferator-activated receptor-α and -γ, and G-protein–coupled receptor. A complex interplay with other pathways exists, which can lead to the synthesis and degradation of prostaglandins and other bioactive lipids such as palmitoyl ethanolamide and anorexigenic oleoyl ethanolamide. Each has actions linked to motility and the inflammatory cascade. A recent article by Srivastava et al. provides a thorough review on this topic (*9*).

EFFECT OF CANNABINOIDS ON GUT MOTILITY

Although decreased gastrointestinal motility due to cannabinoids has been established in both human and experimental animal models, it has not been definitively established in cannabis users with gastroparesis. To clarify these potentially discordant findings, we will examine the literature.

In Vitro and In Vivo Studies

In vitro studies have demonstrated a physiologic braking effect of tetrahydrocannabinol on gastrointestinal and colonic motility (*10*). Decreased smooth muscle contractility and peristaltic action are the result of CB1 receptor activation by tetrahydrocannabinol, resulting in the inhibition of acetylcholine neurotransmitter release. In vivo animal studies validated these findings by measuring intragastric pressures and the gastrointestinal transit times of radiopaque or radiolabeled meals (*11*). In a mouse model of terminal ileitis, CB1 receptors are overexpressed, thereby decreasing motility. It is hypothesized that this upregulation of CB1 receptors is a protective mechanism regulated by the endocannabinoid system to counteract the pathophysiologic hypermotile state, which defines inflammatory bowel disease and possibly other functional disorders of the gut such as irritable bowel syndrome (*12*). Relaxation of the lower esophageal sphincter is also inhibited by tetrahydrocannabinol, preventing gastroesophageal reflux (*13*).

Human Experimental Studies

Only 2 double-blind, experimental studies conducted in 1990 and 2006 validated delayed gastric emptying in healthy volunteers after oral tetrahydrocannabinol intake by scintigraphy (*14*,*15*). Of note, both studies predate the current procedural standards for gastric emptying. As such, they used different imaging times (2-h vs. 6-h endpoints) and different standard solid meals (cooked chicken liver, beef stew, crackers, and water vs. eggs, buttered toast, and 1% milk). Both studies were also limited by a small sample size (n = 13 and 30), with results applicable to the measurable effects of only orally ingested dronabinol–tetrahydrocannabinol at dosages prescribed for antiemetic use. The study with 13 healthy volunteers (*15*) demonstrated statistically significant delays in gastric emptying at 30 min and 2 h. The greatest difference was detected at 2 h, with a 40% increase in average percentage retention (45.6% ± 7.2% vs. 73.9% ± 7.1%). The study with 30 volunteers (*14*) demonstrated a weaker but statistically significant delay in gastric emptying evidenced by an increased half-time over a 6-h time frame (150 ± 6 vs. 175 ± 11). Post hoc analysis showed that the delays were significant only among women, for which there is no clear explanation.

Human experimental research has failed to definitively establish a significant measurable effect of cannabinoids on small- or large-bowel transit (*14*). Future research that focuses on cannabis users is necessary. Small- and large-bowel transit scintigraphy is infrequently encountered in daily practice but could be used to measure the effect of novel selective cannabinoid therapies designed for disorders of hyper- or hypomotility such as irritable bowel syndrome (*13*). At present, conditions that are characterized by abnormal small- or large-bowel motility, such as celiac disease, small-intestinal bacterial overgrowth, and inflammatory bowel disease, are more commonly evaluated with fluoroscopy or CT/MR enterography. However, these studies lack the dynamic, quantitative, functional assessment ascertained by scintigraphy (*16*).

Gastric Emptying in Cannabinoid Users

Recent cross-sectional studies have examined the prevalence of cannabinoid use in patients with gastroparesis, and no significant difference in gastric emptying times was found between users and nonusers. Two studies benefited from a large sample size (n = 197 and 506) and use of the current Society of Nuclear Medicine and Molecular Imaging procedural standards for GES (*17–19*). Their analysis also considered the effects of cannabinoid type, routes of intake, and chronicity or frequency of use. However, a major limitation of these studies was the lack of a baseline GES before cannabis exposure. This would control confounding variables that may contribute to significant interindividual differences in gastric emptying times. A population-based study comparing rates of gastric emptying among states or countries with a higher incidence of cannabis exposure could be informative and establish an association but not causality (*20*). Additionally, the reference ranges for GES may be unique for certain populations because of population genetics or unique gut microbiota cultivated by region-specific foods and dietary habits (*21*).

Perceived Benefits of Cannabis for Gastroparesis

Perhaps the most interesting result comes from a recent large National Institutes of Health–sponsored trial in which 81% of cannabis users perceived benefits in their gastroparesis

symptoms. The investigators reported that cannabis users represented a minority of all gastroparesis patients (12% of 506 patients) and had higher baseline scores for nausea, vomiting, and upper abdominal pain. There are 2 possible explanations for these findings—that is, either cannabis causes more severe gastrointestinal symptoms or gastroparetic patients with worse symptoms were prone to use cannabis. A baseline symptom inventory before cannabis exposure may have clarified the temporal relationship (*19*).

Further evidence that supports the clinical benefit of cannabis comes from a small prospective cohort study ($n = 24$) by Barbash et al. (*22*). Patients with delayed gastric emptying by GES were selected and prescribed dronabinol–tetrahydrocannabinol, medical cannabis, or both via vaporized inhalation or sublingual drops. The tetrahydrocannabinol-to-cannabidiol ratio of the medical cannabis was determined by the dispensary for each patient and not considered in the analysis. A significant improvement was found in abdominal pain and all symptoms measured by the Gastroparesis Cardinal Symptom Index. Key limitations were small sample size and the lack of a placebo-controlled masked study design. Additionally, because the study could not control the highly variable ratios of tetrahydrocannabinol to cannabidiol prescribed to patients by dispensaries, the treatment effect is difficult to measure and cannot be attributed to a particular cannabinoid (tetrahydrocannabinol vs. cannabidiol). The lack of standardization inherent in the heterogeneous cannabis marketplace limits the analysis. Additionally, a follow-up GES at the time of symptom improvement was unfortunately not performed (*22*).

The seemingly contradictory cannabinoid effects that improve gastroparetic symptoms but likely delay gastric emptying have yet to be elucidated. Experts hypothesize that these perceived benefits are unrelated to effects on gastric emptying via CB1 receptors but are instead the result of tetrahydrocannabinol or cannabidiol action on other cannabinoid receptors that blunt visceral sensation possibly via CB2 receptor activation. To clarify these questions, a recent study evaluated the efficacy of cannabidiol in patients with gastroparesis and demonstrated a significant improvement in symptoms despite slower GES times. However, the same researchers using a near-identical study design to evaluate patients with functional dyspepsia and normal baseline GES failed to demonstrate a significant change in GES times. No such randomized controlled trial exists for a tetrahydrocannabinol treatment group. Regardless, any measurable treatment effects discovered by a randomized controlled trial would be limited to a specific patient population treated with pharmaceutical cannabinoid formulations. It would be inappropriate to extrapolate the results to commercial cannabis use comprising a diverse cannabinoid marketplace with heterogeneous tetrahydrocannabinol and cannabidiol potencies, variable pharmacokinetic profiles dependent on route of intake, and individualized gut microbiota (*23–25*).

Cannabinoid Hyperemesis Syndrome

Chronic heavy cannabinoid intake can result in a clinical syndrome characterized by bouts of cyclic hyperemesis and relieved by prolonged hot baths or showers. An increase in incidence has been attributed to the expanding access to cannabis nationwide. Originally characterized as a subtype of cyclic vomiting syndrome because of overlapping features, it is now separately defined by the Rome IV criteria. Cannabinoid hyperemesis syndrome may be distinguished by delayed gastric emptying compared with the rapid gastric emptying of cyclic vomiting syndrome (*26*,*27*).

Despite the strong correlation between frequent cannabis use and cannabinoid hyperemesis syndrome, a case series by Simonetto et al. demonstrated that only 30% of 98 patients had delayed gastric emptying, whereas 45% had normal emptying and 25% had rapid emptying (*28*). Such paradoxical findings underscore the perplexing relationship between cannabis and potentially delayed gastric emptying among chronic users.

From a technical perspective, the timing of scintigraphy relative to cannabis intake may also contribute to inconsistent results. It is plausible that the timing of GES acquisition may be stalled for patients who have hyperemesis because they cannot tolerate the radiolabeled meal or in whom radioactive contamination from uncontrolled hyperemesis needs to be avoided. With the 4-h half-life of tetrahydrocannabinol, it is possible that the GES may not capture the delayed gastric emptying that had been present at initial presentation. The initial human experimental studies that reported delayed gastric emptying in healthy subjects started GES within 1 h of dronabinol–tetrahydrocannabinol administration. Follow-up GES in patients with delayed gastric emptying after cannabis cessation would help clarify these findings. In the initial case series, in which Allen et al. described cannabinoid hyperemesis syndrome, the single patient who demonstrated severely delayed gastric emptying was the only patient evaluated during an acute episode (*29*). The other patients demonstrated normal gastric emptying when evaluated between bouts of illness. Regardless, the diagnosis of cannabinoid hyperemesis syndrome should be based on drug history, symptomatology, and resolution of symptoms after cessation rather than GES.

THERAPEUTIC POTENTIAL OF ENDOCANNABINOID SYSTEM

The endocannabinoid system plays a crucial role in maintaining gastrointestinal balance and has therapeutic potential. Cannabinoids have demonstrated antiinflammatory and pain-relieving properties and may benefit patients with gastrointestinal conditions, as suggested by small studies on patients with inflammatory bowel disease. However, findings from epidemiologic studies contradict some animal and human research, particularly regarding potential benefits in obesity, fatty liver, gastroparesis, and irritable bowel syndrome. These inconsistencies highlight the complex

interactions between the endocannabinoid system and other systems such as the gut microbiome. Current studies focusing mainly on CB1 and CB2 receptors and exploring substrates responsible for the synthesis and degradation of endocannabinoids could open new therapeutic possibilities (*17*,*23*).

DRUGS AND BUGS: CANNABINOIDS AND GUT MICROBIOME

Further complicating our understanding of the endocannabinoid system is its relationship to the gut microbiome (Fig. 1). The gut microbiome has emerged as a key component of human health in recent years, with far-reaching effects on nutrition, cancer susceptibility, and gastrointestinal disorders, among others. Consumers are inundated by marketing which claims that pre- or probiotic products will enhance our health through recolonization of healthy gut flora. Although the efficacy of these products is debated, there is a plethora of evidence demonstrating that the microbiome in our gut does impact our health. The homeostatic imbalance between the microbiome and the human host is termed dysbiosis as opposed to the ideal state of symbiosis (*9*). A recent large systematic review found that nearly half of patients with gastroparesis are also affected by small-intestinal bacterial overgrowth, further strengthening the connection between motility and the gut microbiome (*30*).

The endocannabinoid system, which links the gut to the brain, is affected by the gut microbiome. It is postulated that their interaction occurs via 3 pathways: the hypothalamic–pituitary–adrenal axis, the vagus nerve, and systemic neurotransmitter–hormonal regulation. Researchers have validated these relationships by measuring changes in endocannabinoid tone after introducing specific bacteria to germ-free mice. Manipulation of gut microbiota through antibiotics, probiotics, a high-fat diet, and gene-knockout expression results in alterations of endocannabinoid levels (anandamide and 2-archidonoyl glycerol) and cannabinoid receptor expression. Conversely, the opposite is true when endocannabinoid tone is manipulated, thereby altering microbiota composition. Even more astounding, researchers have discovered receptor sites on bacteria (e.g., *Helicobacter pylori, Escherichia coli,* and *Pseudomonas aeruginosa*) that respond to human neurotransmitters (epinephrine, norepinephrine serotonin), hormones (gastrin, somatostatin, insulin, steroids), and immune factors resulting in measurable changes in microbiota composition and virulence, reinforcing the bidirectional aspect of the gut–brain–microbiome axis (*31*,*32*). Mouse models can mimic a variety of pathophysiologic disease states, thereby enabling researchers to study the effect of microbiota in inflammatory conditions, metabolic disorders, and stress (*9*). Although this research is limited to endocannabinoid signaling, phytocannabinoids likely have a similar effect given their shared receptors. Animal models and human cross-sectional studies have successfully demonstrated alterations in gut microbiota caused by phytocannabinoid exposure. More importantly, inflammatory markers and clinical symptoms were improved after correction of the pathologic dysbiosis in animal models (*33*–*35*).

The highly personalized microbiota among individuals, cultures, and geographic regions could significantly impact the effect of cannabinoids. In the age of precision medicine, emerging technologies that rely on big data attempt to uniquely characterize an individual's microbiome (*36*). Researchers have identified unique subpopulations of microbiota along different segments of the gastrointestinal tract within single individuals and have expanded their work to characterize the gut virome (*37*,*38*). Continued advances within molecular imaging such as attempts to radiolabel microorganisms may allow us in the future to visually assess the collective function of our gut flora (*39*). One could postulate that careful selection of one's diet could cultivate gut microbiota optimized for desirable therapeutic effects.

THE MUNCHIES

This article would not be complete without a discussion of the well-known phenomenon of a surge in appetite and food consumption after cannabis use, colloquially known as the munchies. Tetrahydrocannabinol activates CB1 receptors in the brain, thereby increasing appetite and the desirability of food. This homeostatic balance is regulated by the endocannabinoid system's action on the hypothalamus, which modulates the hunger hormones ghrelin and leptin. Ghrelin stimulates appetite and increases motility, whereas leptin curbs hunger and decreases motility. Because endocannabinoids exert their action on the upstream hypothalamic homeostatic regulator, it is possible that the interaction between exogenous cannabis exposure and the native endocannabinoid system could produce both promotile and antimotile effects depending on the incompletely understood physiologic feedback loop (*40*,*41*). Cannabinoids also act on pleasure pathways in the brain that increase dopamine and result in the characteristic insatiable hunger. An animal study looked at the relationship between different macronutrient stimuli and endocannabinoid signaling in mice. They found that endocannabinoid levels highly regulate dietary fat intake, whereas no measurable response was identified in carbohydrate- or protein-based meals. These effects have led to medications that either stimulate or block cannabinoid signaling. At present, they can be prescribed as an appetite stimulant in anorexic patients. CB1 receptor antagonists have been tried for weight loss in obesity but were stopped because of severe neuropsychiatric side effects (*15*,*42*).

HIGH-YIELD CLINICAL CONSIDERATIONS IN NUCLEAR MEDICINE

There is limited evidence that cannabinoids result in significant delays in gastric emptying. Any significant delays would likely be limited to instances of very recent intake ($<$12 h). The social history should be reviewed for all forms of cannabinoids (medical or recreational marijuana,

dronabinol–tetrahydrocannabinol, synthetic cannabinoids such as K2 or Spice). To avoid false-positive results, it is recommended to avoid cannabinoid intake for at least 72 h before GES, although no cannabis after midnight would likely suffice (*43*). This measure is conservative and extends several half-lives beyond the 4-h serum half-life of tetrahydrocannabinol. Cannabinoids should be added to the list of medications that may affect gastric emptying per the Society of Nuclear Medicine and Molecular Imaging procedure standards for GES.

If GES is requested for a chronic cannabis user, it is important to recognize that a negative result is more helpful. In patients with gastroparetic symptoms and a normal GES result, other functional gastrointestinal disorders should be considered such as functional dyspepsia. If the result is positive, cannabis may or may not contribute to the result and should be correlated with the timing of intake. The collective research does not suggest a significant difference in gastric emptying times in chronic users. A trial of prolonged cessation to assess improvement in symptoms and repeat GES could be considered. If gastroparetic symptoms improve with cannabis, abnormal GES times should yield to symptom index scoring systems as the primary measure of treatment effect.

GES has limited utility in differentiating cannabinoid hyperemesis syndrome from cyclic vomiting syndrome. Rapid gastric emptying is more characteristic of cyclic vomiting syndrome but should serve only as a supporting criterion given the significant overlap of GES times between the two conditions. A history of cannabis use and resolution of symptoms after cessation are the primary differentiating diagnostic features of cannabinoid hyperemesis syndrome.

Cannabinoids should be suspended before small- or large-bowel transit studies to avoid false-positive (slow transit) results, unless measuring the cannabinoid effect is the purpose of the examination. Although this issue is incompletely studied, our current understanding is that cannabinoids could decrease bowel motility and thereby increase transit times. The effect on transit times in chronic users is currently unknown.

CONCLUSION

Given the increased availability of medical and recreational cannabis nationwide, its effects on bowel motility and inflammatory bowel disease have garnered significant attention. Historically, cannabis has been associated with decreased gastrointestinal motility, although recent research strongly suggests a paradoxical clinical improvement in gastroparesis. At present, there is no convincing evidence that cannabis results in significant delays in gastric emptying. More robust double-blinded trials that use the GES procedure standard, test various cannabinoid intake types at different time intervals, and enroll both naïve and chronic users could help clarify the relationship under specific experimental conditions. However, the generalizability of the results would be significantly limited when considering the heterogeneous cannabinoid marketplace accessible to our patients. Instead, studies that assess its clinical utility in symptom management would be of greater utility. We are just beginning to understand the complex interplay among other phytocannabinoids (cannabidiol), endocannabinoids (anandamide and 2-archidonoyl glycerol), and CB1 and CB2 receptors within the broader endocannabinoid system. The multifaceted effect on the gut–brain–microbiome axis requires further research within each of these domains to decipher its many potential benefits on the gut.

DISCLOSURE

Mary Beth Farrell is an employee of the IAC. The views expressed are those of the authors and do not reflect the official policy or position of Brooke Army Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Army, the Department of Defense, or the U.S. government. No other potential conflict of interest relevant to this article was reported.

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